REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on July 2, 2003 and allowance of the application.

Applicants also request acknowledgment of the Drawings submitted at the time of filing.

Claims 3-9, 13-16, 24, 33-38, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The rejection states that the claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection states that the instant claims are drawn to the "prevention" of male erectile dysfunction (MED). The rejection states that the instant specification does not provide information for one of skilled in the art to "prevent" MED in patients that are not suffered from it. The rejection states that the term "prevent" is construed as an absolute prevention for MED. The rejection states that it is known in the art that impotence has numerous etiologies such as alchoholism, neurogenic disorders, intrappsychic factors including abnormal fear of vagina, sexual guilt, depression, and fear of intamacy (See Merck Manual, 16th ed., 1992, pages 1575-1576). The rejection states that the instant specification does not provide sufficient guidance as to how to keep the etiologies from being manifested into MED.

Claims 3-9, 13-16, 24, 33-38, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for falling to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection states that the expression "inhibitor has no, or substantially no, activity towards endopeptidase NEP and/or angiotensin converting enzyme" in claim 4 renders the claim indefinite as to the degree of activity towards endopeptidase NEP and/or angiotensin converting enzyme. The rejection states that it is not clear what inhibitors would be encompassed by the claim.

The rejection states that claim 5 is not understood because it is not clear what the term "selective" referred to. The rejection questions whether the NPY

inhibitor is being selective? Or the patients as selective? It is confusing.

The rejection states that the expression "NPYi when in use is selective for an NPY associated with male genitalia" recited in claim 13 renders the claims indefinite. The rejection states that it is not clear what NPY is considered as associated with male genitalia and therefore, it is not clear what NPY inhibitors are encompassed by the claims.

The rejection states that the expression "NPYi that is capable of selectively increasing the intracavernosal pressure" in claim 15 renders the claim indefinite as to what NPY inhibitors are encompassed by the claims and the rejection asks the questions: What NPY inhibitors are considered as NP inhibitors that selectively "increase the intracavernosal pressure"? And what NPY inhibitors will not selectively "increase the intracavernosal pressure"? The rejection states that the metes and bounds of the claim are not defined.

The rejection states that a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The rejection notes the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 ISPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where braod language is followed by "such as" and then narrow language. The rejection notes the Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. The rejection also notes also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche,* 86 USPQ 481 (Bd. App. 1949). The rejection states that in the present instance, claim 33 recites the broad recitation "abnormal drink and food intake disorders", and the claim also recites "obesity, anorexia, bulimia and metabloic disorders" which is the most norrower statement of the range/limitation.

Applicants traverse the rejection of the claims (as amended) under 35 U.S.C. 112.

Applicants have amended the claims by replacing the abbreviation "MED" with the term male erectile dysfunction.

Applicants have deleted the term "prevent" to emphasize the term "treat".

Applicants have deleted the term "substantially no" in claim 4 thus obviating the rejection.

Applicants have amended claim 5 to clarify that the NPY Y1 inhibitor is selective.

Applicants submit that the phrase "NPYi when in use is selective for an NPY associated with male genitalia" is definite. However, in the interests of expediting prosecution Applicants have amended claim 13 to clarify it. The phrase as amended reads "NPYi when in use is selective for an NPY receptor associated with male genitalia" (underline denotes amendment). Support for the addition of the word receptor may be found on page 4, lines 23-26. Applicants submit that this amendment more accurately reflects their intent.

The term "NPYi that is capable of selectively increasing the intracavernosal pressure" is clear to one skilled in the art. The rejection questions how one would know whether a NPY inhibitor selectively, or does not selectively increase the intracavernosal pressure. Applicants submit that one would perform standard tests known to those skilled in the art to make such determinations. An example of such a test is described in the specification on pages 120 and 121.

Applicants have amended claim 33 to delete the exemplary disease/conditions.

Claims 3-9, 13-16, 24, 33, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hutchison et al. (WO 98/03492) and Gregor et al. (WO 98/07420).

The rejection states that Hutchison et al. teaches a new class of neuropeptide Y1 specific ligands. The rejection states that Hutchison et al. also teaches a method of treating disorders associated with an inappropriate stimulation of neuropeptide Y receptors, including diseases related to sexual

dysfunction and reproductive disorders, and abnormal drink and food intake such as obesity, anorexia, bulimia, and metabolic disorders (See page 9, lines 6-9 and 26-28 in particular). The rejection states that Hutchison et al. teaches the composition comprising the Neuropeptide Y1 antagonist is useful for oral, topical, parenteral administration (See page 11, lines 3-4).

The rejection states that Gregor et al. teaches compound F50 of the instant application as regulators of NPY activity (See page 15 and abstract in particular), that Gregor et al. further teaches that the compound is useful as a feeding suppressant (See page 19, lines 3-5), and that Gregor et al. further teaches that these compositions, which possess vasodilating activites and are capable of beneficially affecting the reperfusion of ischemic organs, can be administered orally, topically and locally (See page 19, lines 3-5 and 11-20, in particular).

The rejection admits that the references do not expressly teach the neuropeptide inhibitors can increase the intracavernosal pressure. The rejection states that the references do not teach the herein claimed timing of dosing (i.e., before or during sexual arousal).

The rejection reasons that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the neuropeptide Y inhibitors of Hutchinson et al. or Gregor et al. in a method of treating MED by increasing the intracavernosal pressure.

The rejection states that one of ordinary skill in the art would have been motivated to the neuropeptide Y inhibitors of Hutchinson et al. or Gregor et al. in a method of treating MED by increasing the intracavernosal pressure because the neuropeptide Y inhibitors of Hutchinson et al. or Gregor et al. are known to be useful to increase the blood flow perfusion. The rejection states that increasing blood perfusion in the male genitalia would cause the increase of intracavernosal pressure and thereby cause an erection. The rejection states that F50 is the exemplified neuropeptide Y inhibitor and therefore considered as possessing the herein claimed characteristics (i.e., selective in NPY associated or located with male genitalia, having no, or substantially no, activity towards endopeptidase NEP and/or angiotensin converting enzyme of NPY inhibitor).

The rejection concludes that one of ordinary skill in the art would have been motivated to administer the NPY inhibitors of Hutchinson and Gregor in the treatment of MED before or during sexual arousal. The rejection notes that optimization of dosage regimen is considered as within the purview of a skilled artisan.

Applicants traverse the rejection of claims 3-9, 13-16, 24, 33, and 44 under 35 U.S.C. 103(a) as being unpatentable over Hutchison et al. (WO 98/03492) and Gregor et al. (WO 98/07420).

Applicants submit that a conclusion of prima facie obviousness cannot be supported on the present record.

The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Laskowski, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

The rejection does not detail reasoning that provides the motivation to modify the prior art and thus the rejection does not present a *prima facie* case of obviousness. Specifically, for example, the rejection does not detail reasoning to use an NPY inhibitor for male erectile dysfunction, as distinct from sexual dysfunction. Further the rejection does not detail reasoning to use an NPY inhibitor for male erectile dysfunction in light of the implication in the references that an NPY inhibitor would not restrict blood flow from the penis resulting in detumesence as further described below.

Further, Applicants submit that even assuming arguendo (which Applicants do not admit) that the references relied on by the Examiner make Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. The Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the references provide no effective motivation or suggestion that an NPY inhibitor could or should be tried in the treatment of male erectile dysfunction (as distinct from sexual dysfunction) and (2) even allowing, *arguendo*, that any such suggestion or motivation were found

in these references, the references provide no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants also respectfully refer the Examiner to the MPEP, Section 2142, where the legal concept of prima facie obviousness is explained in detail with applicable illustrations and cited authority. As stated there:

1. The concept of prima facie obviousness is a "procedural tool of examination" which "allocates who has the burden of going forward with production of evidence in each step of the examination process".

2. The Examiner "bears the initial burden of factually supporting any prima facie conclusion of obviousness;

3. If the Examiner "does not produce a prima facie case, the Applicant is under no obligation to submit evidence of nonobviousness"; and

4. In determining whether a prima-facie case of obviousness exists, the Examiner is cautioned that "impermissible hindsight must be avoided and the legal conclusion [of prima facie obviousness] must be reached on the basis of the facts gleaned from the prior art".

MPEP Section 2142 further advises as follows regarding what is required before the Examiner can establish prima facie obviousness:

"To establish a prima facie case of obviousness, three basic criteria must

be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or referernces when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure." (underlining added for emphasis)

Accordingly, the threshold issue becomes whether the Examiner has carried his burden to establish prima facie obviousness from the cited references-- is there something in the art that motivates one skilled in the art to try to use an NPY inhibitor for the treatment of male erectile dysfunction and if so would their be a reasonable expection of success. Again, Applicants submit that the Examiner has not carried the burden to establish a prima facie case of obviousness.

Applicants submit that there is no motivation in Hutchison et al. or Gregor et al. to use their compounds to treat male erectile dysfunction. Applicants submit that the following statements in the Office Action are inaccurate.

1. "that one would have been motivated to use the neuropeptide Y inhibitors of Hutchinson et al. or Gregor et al. in a method of treating MED by increasing the intracavernosal pressure because the neuropeptide Y inhibitors of Hutchinson et al. or Gregor et al. are known to be useful to increase the blood flow perfusion."

2. "Increasing blood perfusion in the male genitalia would cause the increase of intracavernosal pressure and thereby erection. "

An increase in intracavernosal pressure requires two actions -increased blood flow to the penis and restriction of blood flow out of the penis. An increase of blood flow perfusion does not suggest any impact on the restriction of the flow of blood out of the penis which is a necessary part of an erection. Thus, there is no motivation in Hutchison et al. or Gregor et al. to use their compounds to treat male erectile dysfunction i.e., achieve erections. Nor does an increase in blood

perfusion provide a reasonable expectation of success for the treatment of male erectile dysfunction.

Thus, Applicants submit that the references actually teach away from their claimed invention. Because the references teach away there is neither the motivation to try NPY inhibitors for the treatment of male erectile dysfunction nor the reasonable expection that an NPY inhibitor would be effective for the treatment of male erectile dysfunction. Applicants recited the general state of the art in their specification page 7, lines 8-11 "...The reported function of NPY in the penis is its role in the venous occlusion mechanism that occurs at penile level to sustain erections. That is to say, it has been reported that NPY acts as a vasoconstrictor and causes restriction of penile veins, in particular those which regulate the flow of blood from the penis..." Applicants submit that this general state of the art teaches away from their claimed invention since an inhibitor of NPY would be expected to have the opposite impact.

As regards the references cited by the Examiner the general vaso-action of NPY is detailed in Hutchison et al. and Gregor et al. In particular, Hutchinson et al. refers to the vasoconstrictive action of NPY. Thus one skilled in the art would learn from a review of Hutchinson that an NPY inhibitor would have the converse effect to the NPY ligand (vasoconstrictor) i.e. act as a vasodilator. Restated, Hutchison et al. implies that vasodilation would be the result of a NPY inhibitor. Specifically, page 1, lines 14 and 15 of Hutchinson et al. states that "...Various animal studies have shown that activation of Neuropeptide Y1 receptors is related to vasoconstriction..." Further, page 1, lines 22 and 23 of Hutchinson et al. states that "...Neuropeptide Y is a powerful stimuli of food intake, and an inducer of vasoconstriction leading to hypertension...".

Also, Gregor et al. states on page 19, lines 3 and 4 that the compounds of the patent application are useful as "...vasodilating agents to beneficially affect the reperfusion of ischaemic organs...". Since Gregor et als' compound is a NPY regulator resulting in vasodilation the reference merely reinforces the teaching of Hutchinson et al.

The art when taken as a whole is even more specific regarding NPY's action on the flow of blood in the penis. As specifically applied to the genitalia,

representative examples of the art (e.g., Journal of Urology 1991 Jun; 145(6):1292-6; Progress in Neurobiology, Vol. 47, pp. 235 to 255, 1995) teach that the role of NPY in the penis is to cause restriction of the penile veins, preventing or reducing the flow of blood from the corpus cavernosum in the penis, thereby aiding maintenance of an erection.

> Page 1294 of the J Urol. paper cited above states "In the deep dorsal vein, NPY may have a prolonged contractile response to nerve stimulation due to its medial innervation and, further, may potentiate the vasoconstriction caused by noradrenaline release since DBH-immuno-reactive nerves are found around the adventitial-medial border. These actions may play an important role in penile erection, since venous occlusion is necessary to prevent drainage of the cavernous spaces because this occurs principally in the large penile veins."
>
> Pages 240 and 241 of the Progress in Neurobiology paper cited above states that the local effect of NPY on penile tissues is contraction (see Table 3).

Conversely, the art would imply that if a NPY inhibitor were administered, the expected result would be relaxation of the penile veins (resulting in flow of blood from the corpus cavernosum) and detumescence of the penis, i.e., maintainance of the penis in its flaccid state. Clearly this does not provide the motivation to use a NPY inhibitor for the treatment of erectile dysfunction nor does this provide a reasonable expectation of success that a NPY inhibitor would be useful for the treatment of erectile dysfunction.

In contrast, Applicants have surprisingly found that, contrary to the suggestion in the art, the administration of a NPY inhibitor results in an increase in intracavernosal pressure (in contrast to the expected detumescence described immediately above) and facilitation of penile erection. The increase in intracavernosal pressure means that the administration of an NPY inhibitor allows both increased blood flow to the penis and restricts blood flow out of the penis.

Restated, the art would suggest an NPY inhibitor would allow blood flow out of the penis in contrast to both the facilitation of increase blood flow to the penis and restriction of blood flow out of the penis resulting from Applicants' invention. Applicants' note the admission in the Office Action that the

references do not expressly teach that neuropeptide inhibitors can increase the intracavernosal pressure.

Claims 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hutchinson et al. and Viagra monograph, June 1999.

The rejection states that Hutchinson et al. teaches a new class of neuropeptide Y1 specific ligands. The rejection states that Hutchinson et al. also teaches a method of treating disorders associated with an inappropriate stimulation of neuropeptide Y receptors, including diseases related to sexual dysfunction and reproductive disorders, and abnormal drink and food intake such as obesity, anorexia, bulimia, and metabolic disorders (See page 9, lines 6-9 and 26-28 in particular). The rejection also states that Hutchinson et al. teaches the composition comprising the Neuropeptide Y1 antagonist as useful for oral, topical, parenteral administration (See page 11, lines 3-4).

The rejection states that the Viagra monograph teaches Viagra as a PDE5 inhibitors useful for treating erectile dysfunction and can be administered orally (See page 2381, col. 3 Clinical Pharmacology Section; page 2384, Dosage and Administration Section).

The rejection admits that the references do not expressly teach the use of both a NPY inhibitor and a PDE5 inhibitor together in a method of treating MED.

The rejection reasons that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ both a NPY inhibitor and a PDE5 inhibitor together in a method of treating MED.

The rejection concludes that one of ordinary skill in the art would have been motivated to employ both a NPY inhibitor and a PDE5 inhibitor together in a method of treating MED. The rejection states that it is known in the art that both a NPY inhibitor and a PDE5 inhibitor are useful in treating MED individually. The rejection also concludes that therefore, combining two agents, which are known to be useful to treat MED individually into methods useful for the very same purpose is *prima facie* obvious (See *In re Kerkhoven* 205 USPQ 1069).

Applicants traverse the rejection of claims 34-38 under 35 U.S.C. 103(a) as being unpatentable over Hutchison et al. (WO 98/03492) and the Viagra monograph, June 1999.

Applicants submit that for at least the reasons detailed above claims 34-38 are not obvious over Hutchison et al. and the Viagra monograph. Thus, for example, the Viagra monograph does not compensate for the deficiencies of the Hutchison et al. reference as regards the use of NPY inhibitors to treat male erectile dysfunction.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

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